Brief report

Intra-and inter-analyzer imprecision of cell population data on Sysmex XN-10

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Article Info

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Abstract

Introduction: Cell population data (CPD) derived from modern hematology analyzers provide morphological and functional insights into leukocytes beyond traditional cell counts. Nevertheless, their introduction into clinical practice requires proven analytical precision and consistency across instrumentation.

Method: Two K2EDTA blood samples (one from a healthy blood donor and one from an intensive care unit patient) were analyzed in ten replicates on two Sysmex XN-10 analyzers. Intra- and inter-analyzer imprecision were calculated as coefficients of variation (CV%).

Results: Intra-analyzer CV% ranged from 0.2–7.9% and inter-analyzer CV% from 0.6–9.8%. For neutrophil, lymphocyte, and monocyte CPD parameters, intra-/inter-analyzer CV% were 0.2–2.5%/0.6–7.0%, 0.5–6.6%/0.7–7.2%, and 0.2–7.9%/0.8–9.8%, respectively. The mostly used CPD parameters NE-SFL (neutrophil fluorescence intensity) and MO-X (monocyte complexity) displayed very low imprecision, with intra-analyzer CV% of 0.7–0.9% and 0.2–0.5%, and inter-analyzer CV% of 0.9–1.1% and 0.8–1.7%, respectively.

Discussion: Our results confirm excellent reproducibility of Sysmex XN-10 CPD, consistent with or even improving upon earlier data obtained with the previous Sysmex XN-9000. The very low intra- and inter-analyzer variability of NE-SFL and MO-X supports their use as reliable clinical parameters, especially for infection and sepsis diagnostics.

Introduction

The clinical use of cell population data (CPD) has contributed to reshape the interpretation of routine hematological tests in recent years, providing a more comprehensive view of leukocyte phenotypes beyond simple quantitative cell counts. Rather than merely enumerating white blood cells, advanced hematology analyzers are now capable to identify subtle variations in cell size, internal complexity and nucleic acid content, parameters that mirror the activation state, heterogeneity and functional dynamics of immune cells [1]. Since these measurements are automatically generated alongside standard complete blood cell counts (CBCs), without requiring additional sampling or cost, CPD represent a readily available and cost-effective diagnostic tool across a broad range of clinical contexts [1].

In patients with infectious diseases, mounting evidence suggests that CPD can aid in early detection of bacteremia and sepsis [1]. A recent study using Sysmex XN analyzers showed that the neutrophil fluorescence distribution parameter (NE-WY) displayed a strong discriminative power for diagnosing patients with bacteremia, with an area under the receiver operating characteristic curve (AUC-ROC) of 0.77 [2]. Another investigation in patients with acute infections showed that both the NE-WY and neutrophil fluorescence intensity (NE-SFL) differed significantly between bacteremic and non-bacteremic individuals (ROC-AUC: 0.708 and 0.685, respectively), and the values of both parameters were significantly correlated with bacterial load ($r=0.374$, $p<0.01$ and $r=0.384$, $p<0.01$, respectively) [3]. In another study evaluating CPD in septic patients stratified by liver function, NE-SFL and monocyte complexity (MO-X) demonstrated good diagnostic performance in the overall cohort (AUC-ROC: 0.72 and 0.75, respectively) [4]. When analyzed by hepatic status, these parameters achieved markedly higher accuracy in patients with liver impairment (AUC-ROC: 0.89 and 0.95, respectively) compared with those without hepatic dysfunction (AUC-ROC: 0.72 for both) [4]. Promising results were also reported by Urrechaga et al. [5] in differentiating patients with coronavirus disease 2019 (COVID-19) from those with other bacterial or viral infections, with the combination of the neutrophil-to-lymphocyte ratio and CPD achieving 97.7% diagnostic accuracy using principal component analysis.

Beyond infectious diseases, CPD analysis has also shown potential in the evaluation of hematologic disorders such as myelodysplastic syndromes and acute leukemias, where it can assist in disease screening and classification [6,7].

Although CPD holds substantial promise as both a diagnostic and monitoring tool, a number of methodological challenges need to be addressed before they can be reliably implemented in routine clinical practice. It has been earlier reported that pre-analytical factors (e.g., biological variability, differences in sample handling, and type of anticoagulant used for blood collection) can have a significantly influence of CPD [8,9]. Moreover, there is limited information on the intra- and inter-analyzer reproducibility of these parameters using current-generation analyzers, raising concerns about result comparability across different instruments and laboratories. Establishing standardized analytical procedures and reproducibility benchmarks will hence be crucial to ensure consistency and clinical reliability of CPD measurements. To this end, the aim of this study was to evaluate the intra- and inter-analyzer imprecision of CPD generated by the Sysmex XN-10 hematology analyzer.

Materials and Methods

Two patient samples were randomly selected from all routine hematology specimens collected in 3.0 mL K2EDTA blood tubes conveyed to the service of Laboratory Medicine of the University Hospital of Verona for standard CBC analysis. The first sample was obtained from a healthy blood donor showing no abnormalities in the standard laboratory test panel. The second sample was from an intensive care unit (ICU) patient exhibiting markedly elevated C-reactive protein (CRP: 143 mg/L). Immediately after completion of routine analyses (i.e., the CBC), both samples were anonymized and included in this study. On each sample, CPD were assayed in ten replicates on the first Sysmex XN-10 analyzer (XN-1), followed immediately by ten additional replicates on a second Sysmex XN-10 analyzer (XN-2). Imprecision, expressed as the coefficient of variation (CV%), was calculated separately for each analyzer using the respective ten CPD replicate measurements (intra-analyzer imprecision), while inter-analyzer imprecision was calculated from the combined set of twenty consecutive CPD replicate measurements obtained on both XN-10 analyzers on each sample. The whole blood samples used in this study were residuals from routine testing, fully anonymized prior to analysis, so that informed consent was unnecessary. This study was conducted as part of a local validation of CPD for clinical use at the facility, and its protocol was approved by the local Ethics Committee (approval number 971CESC; July 20, 2016).

Results

The results of our study are summarized in Table 1.

Table 1: Intra- and inter-analyzer imprecision of cell population data (CPD) obtained using the Sysmex XN analyzer.

Parameter	Normal sample						Pathological sample					
	Intra-analyzer XNw-1		Intra-analyzer XN-2		Inter-analyzer		Intra-analyzer XN-1		Intra-analyzer XN-2		Inter-analyzer	
	Mean±SD	CV%	Mean±SD	CV%	Mean±SD	CV%	Mean±SD	CV%	Mean±SD	CV%	Mean±SD	CV%
NE-SSC	149.3±0.5	0.30%	151.2±0.4	0.30%	150.2±1.0	0.70%	160.3±0.3	0.20%	162.4±0.3	0.20%	161.4±1.1	0.70%
NE-WX	312.2±4.8	1.50%	303.1±5.2	1.70%	307.7±6.7	2.20%	331.8±4.6	1.40%	324.4±.0	1.50%	328.1±6.1	1.80%
NE-SFL	45.4±0.4	0.90%	46.0±0.3	0.70%	45.7±0.5	1.10%	56.6±0.5	0.90%	56.9±0.4	0.80%	56.7±0.5	0.90%
NE-WY	652.8±13.8	2.10%	605.5±14.4	2.40%	629.2±27.5	4.40%	758.1±6.7	2.20%	733.3±8.9	1.20%	745.7±18.3	2.40%
NE-FSC	87.3±0.4	0.50%	86.4±0.2	0.30%	86.9±0.5	0.60%	97.8±0.3	0.30%	95.8±0.2	0.20%	96.8±1.0	1.10%
NE-WZ	664.2±16.9	2.50%	582.0±12.4	2.10%	623.1±43.7	7.00%	651.1±12.6	1.90%	584.5±2.4	2.10%	617.8±35.6	5.80%
LY-X	78.5±0.4	0.50%	84.4±0.5	0.60%	81.4±3.0	3.70%	81.3±0.6	0.80%	87.1±0.5	0.50%	84.2±2.9	3.50%
LY-WX	550.6±19.0	3.40%	503.8±28.7	5.70%	527.2±33.8	6.40%	463.6±27.7	6.00%	424.5±15.4	3.60%	444.1±29.8	6.70%
LY-Y	67.8±0.5	0.70%	68.6±0.6	0.90%	68.2±0.7	1.00%	78.5±1.0	1.30%	73.2±3.4	4.60%	75.9±3.6	4.80%
LY-WY	849.6±25.1	3.00%	835.3±55.2	6.60%	842.5±43.4	5.20%	867.9±46.4	5.30%	875.5±45.9	5.20%	871.7±46.3	5.30%
LY-Z	60.9±0.3	0.50%	60.4±0.3	0.50%	60.6±0.4	0.70%	61.4±0.4	0.70%	61.1±0.6	1.00%	61.2±0.5	0.90%
LY-WZ	507.7±20.2	4.00%	450.4±17.9	4.00%	479.1±34.4	7.20%	554.2±29.4	5.30%	520.3±29.4	5.60%	537.3±33.9	6.30%
MO-X	117.9±0.4	0.30%	121.7±0.5	0.40%	119.8±2.0	1.70%	124.7±0.6	0.50%	126.6±0.3	0.20%	125.6±1.0	0.80%
MO-WX	256.3±16.9	6.60%	233.2±18.4	7.90%	244.8±21.1	8.60%	258.9±4.0	1.50%	249.3±9.5	3.80%	254.1±8.7	3.40%
MO-Y	107.9±2.0	1.90%	109.0±2.5	2.30%	108.4±2.4	2.20%	94.3±1.0	1.00%	95.4±1.1	1.10%	94.8±1.2	1.20%
MO-WY	710.3±41.0	5.80%	707.7±45.7	6.50%	709.0±43.5	6.10%	790.4±23.5	3.00%	762.4±34.8	4.60%	776.4±32.8	4.20%
MO-Z	70.2±0.9	1.30%	71.4±0.5	0.70%	70.8±1.0	1.30%	66.2±0.4	0.50%	67.3±0.5	0.70%	66.8±0.7	1.10%
MO-WZ	524.0±30.5	5.80%	445.4±22.8	5.10%	484.7±47.6	9.80%	622.5±22.5	3.60%	537.3±20.3	3.80%	579.9±47.7	8.20%

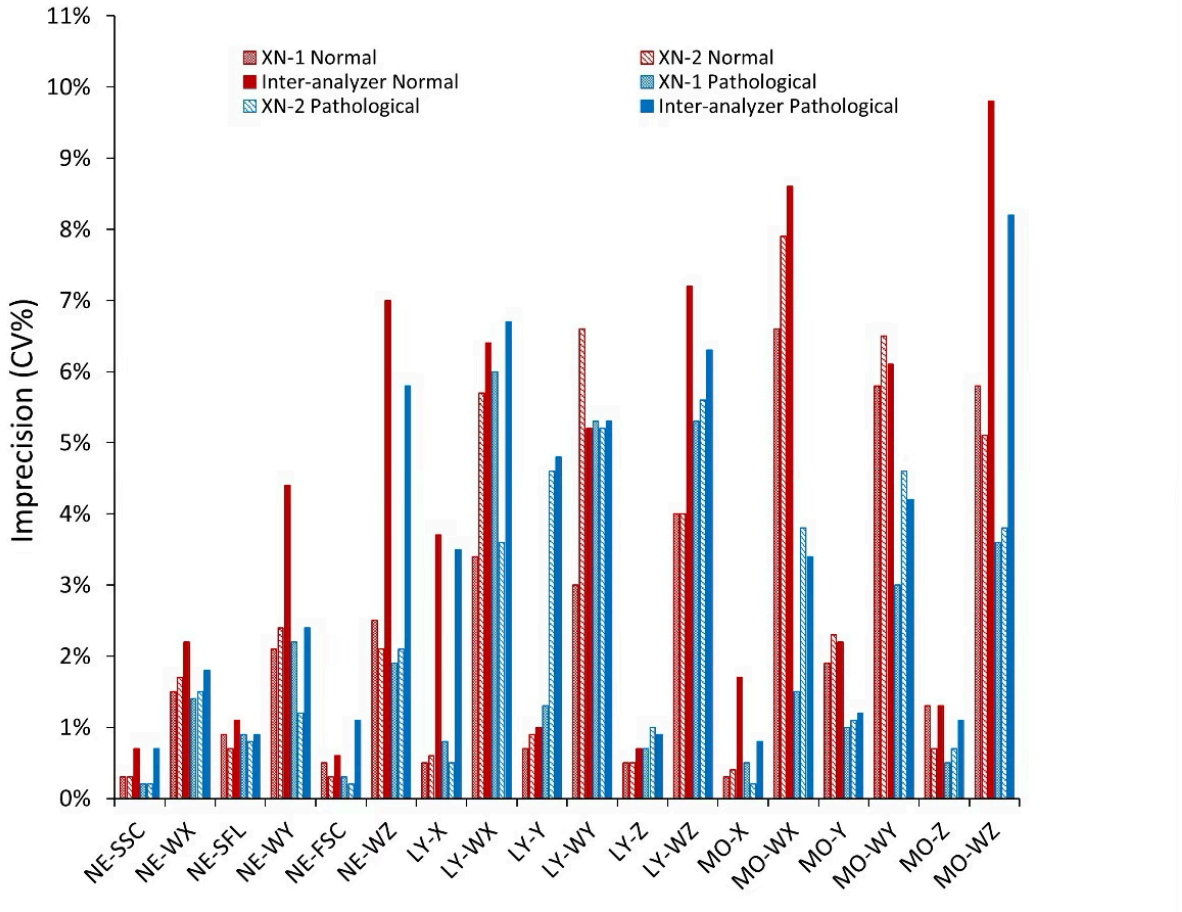
CV%, coefficient of variation; SD, standard deviation

Abbreviations and detailed descriptions of individual parameters are provided in Supplementary Table 1.

The intra-analyzer CV% of CPD on XN-10 ranged between 0.2-7.9% (0.3-7.9% in the normal patient sample and 0.2-6.0% in the pathological patient sample), while the inter-analyzer CV% ranged between 0.6-9.8% (0.6-9.8% in the normal patient sample and 0.7-8.2% in the pathological patient sample).

As concern the specific cell populations, the intra- and inter-analyzer CV% ranged between 0.2-2.5% and 0.6-7.0% for the neutrophil CPD parameters, between 0.5-6.6% and 0.7-7.2% for the lymphocyte CPD parameters, and between 0.2-7.9% and 0.8-9.8% for the monocyte CPD parameters, respectively. Overall, the intra- and inter-analyzer CV% of the mostly used in clinical practice CPD parameters ranged between 0.7-0.9% and 0.9-1.1% for NE-SFL and between 0.2-0.5% and 0.8-1.7% for MO-X, respectively (Figure 1).

Figure 1: Intra- and inter-analyzer imprecision of cell population data (CPD) obtained using the Sysmex XN analyzer.



CV%, coefficient of variation

Abbreviations and detailed descriptions of individual parameters are provided in Supplementary Table 1.

Discussion

Growing evidence supports the use of CPD as valuable tools in evaluation of infectious diseases and other life-threatening conditions, including leukemia and pre-neoplastic syndromes [10]. Nevertheless, before CPD can be routinely implemented in clinical practice, it is essential to verify the consistency and repeatability of measurements both within the same hematology analyzer and across different instruments. This aspect is particularly relevant because modern clinical laboratories often employ multiple, interconnected hematology analyzers operating on the same line [11]. Under such configurations, samples from the same patient, especially those needing frequent retesting, such as in sepsis, may be analyzed by different instruments, making analytical comparability a critical prerequisite for clinical reliability.

The purpose of this study was to evaluate the intra- and inter-analyzer imprecision of CPD parameters generated by the Sysmex XN-10 hematology analyzer, with the objective of assessing their analytical robustness and suitability for clinical application. Overall, intra-analyzer CV% ranged from 0.2 to 7.9%, while inter-analyzer CV% varied between 0.6 and 9.8%, confirming excellent repeatability and reproducibility across instruments. These findings are consistent with, and in most cases superior to, previous data obtained on the earlier Sysmex XN-9000 platform, where within-run CV% were reported between 0.4 and 14.1% [12]. Specifically, neutrophil-related CPD parameters exhibited imprecision between 0.4–5.5%, lymphocyte CPD parameters between 0.7–8.7%, and monocyte CPD parameters between 0.8–14.1%, with good agreement among five different XN-9000 modules.

Among the various CPD parameters, NE-SFL (neutrophil side fluorescence light intensity) and MO-X (monocyte complexity) showed remarkably low intra- and inter-analyzer imprecision, with CV% values consistently below 1.1% and 1.7%, respectively. This degree of analytical precision is excellent for optical and fluorescence-based hematology parameters, strongly supporting their reliability for routine diagnostic use. Such high reproducibility, in fact, provides a solid analytical foundation for clinical implementation, especially in critical care settings where rapid and reliable indicators of immune activation are needed.

The excellent imprecision performance further demonstrates that CPD measurements obtained with the Sysmex XN-10 analyzer are highly robust to inter-analyzer variability, enabling

reliable comparability of results across instruments of the same model and manufacturer. Such reproducibility is essential for standardization within integrated laboratory networks and for broader incorporation of CPD into diagnostic and monitoring algorithms. Although some distribution-width CPD parameters displayed higher CV% values, these remained within acceptable analytical limits for morphological indices and did not compromise interpretive accuracy.

The findings of this study have some important implications for laboratory practice and future research. The low intra- and inter-analyzer imprecision observed supports the robustness of Sysmex XN-10 CPD and strengthens their potential integration into laboratory quality assurance (QA) programs. However, to reach wider clinical implementation, harmonization across different analyzer models and brands will be essential. Variability in optical systems, signal processing, or calibration algorithms may influence CPD comparability, emphasizing the need for multicenter assessments and manufacturer-independent standardization efforts. The excellent precision observed in this study may also have direct implications for laboratory quality control and clinical interpretation of CPD metrics. In particular, parameters such as NE-SFL and MO-X, which demonstrated very low imprecision, could serve as indicators of internal stability within routine hematology quality control programs. The high analytical consistency also supports the use of CPD in longitudinal patient monitoring and automated interpretation algorithms, where minimizing analytical noise is crucial for distinguishing biological changes from technical variations.

Nonetheless, some limitations must be acknowledged. First, the sample size was limited to only two specimens (one from a healthy donor and one from a patient with a marked inflammatory response), selected to represent a biologically relevant range. Although this design allowed an initial assessment of intra- and inter-analyzer imprecision across contrasting physiological conditions, it inevitably underrepresents the biological variability encountered in routine practice. Studies including broader and different sample cohorts, encompassing multiple pathological conditions and demographic categories, would provide a more comprehensive evaluation of CPD variability. Second, even if this study robustly controlled technical sources of variation (e.g., through replicate measurements and standardized analyzer operation), pre-analytical factors, especially sample collection and transportation, could not be experimentally controlled. Finally, the use of residual patient material did not permit inclusion of standardized quality control materials because they currently lack assigned target values for CPD parameters. It is also important to note that potential sources of analytical bias or confounding that may affect CPD repeatability include differences in reagent lots, instrument maintenance status, calibration drift, and environmental conditions such as temperature and humidity. Both Sysmex XN-10 analyzers used in this study were maintained according to the same internal quality standards, operated under identical laboratory conditions, and utilized reagents from the same manufacturing lot, thereby excluding major sources of variability due to these factors.

In conclusion, this study confirms that CPD parameters generated by the Sysmex XN-10 analyzer exhibit satisfactory intra- and inter-analyzer imprecision, with NE-SFL and MO-X emerging as stable and reproducible. These results reinforce the potential of CPD for integration into clinical workflows, particularly for infection and sepsis assessment, where their analytical robustness and previously demonstrated diagnostic value make them powerful tools for precision laboratory medicine.

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Author contributions
Marco Tosi: Development, Investigation. Laura Pighi: Development, Investigation. Mariateresa Rizza: Development, Investigation. Gian Luca Salvagno: Development, Investigation. Giuseppe Lippi: Conceptualization, Data Analysis, Write-up.

Conflict of Interests
None to declare.

Ethics approval
This study was conducted as part of a local validation of CPD for clinical use at the facility, and its protocol was approved by the local Ethics Committee (approval number 971CESC; July 20, 2016).

Consent for Publication
Consent to submit has been received explicitly from all coauthors, as well as from the responsible authorities. Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

Data availability
The data included in this study is available upon request to the corresponding author.

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Supplementary

Supplementary Table 1: Description and clinical significance of leukocytes cell population data (CPD). Adapted from [4].

Parameter	Description	Clinical significance
NE-SSC	Neutrophil cell complexity	Increases when neutrophils contain more granules (e.g., toxic granules), vacuoles, or other cytoplasmic inclusions; decreases with reduced granularity or hypogranulation.
NE-WX	Neutrophil complexity – distribution width	Higher values indicate greater heterogeneity in neutrophil internal structure, relative to NE-SSC.
NE-SFL	Neutrophil fluorescence intensity	Reflects nucleic acid content; higher values suggest increased cellular RNA and DNA, as observed in immature or activated neutrophils.
NE-WY	Neutrophil fluorescence intensity – distribution width	Represents variability in nucleic acid content within the neutrophil population, compared with NE-SFL.
NE-FSC	Neutrophil cell size	Indicates average neutrophil volume; may change in the presence of abnormally large or small cells.
NE-WZ	Neutrophil cell size – distribution width	Higher values indicate a broader size variation within the neutrophil population, compared with NE-FSC.
LY-X	Lymphocyte cell complexity	Increases with the presence of cytoplasmic granules or vacuoles (e.g., large granular lymphocytes).
LY-WX	Lymphocyte complexity – distribution width	Elevated values reflect higher heterogeneity in lymphocyte internal structure, relative to LY-X.
LY-Y	Lymphocyte fluorescence intensity	Correlates with nucleic acid content; elevated in activated, abnormal, or blast-like lymphocytes.
LY-WY	Lymphocyte fluorescence intensity – distribution width	Represents the degree of variability in nucleic acid content among lymphocytes, compared with LY-Y.
LY-Z	Lymphocyte cell size	Indicates average lymphocyte volume; may increase in activated cells or decrease in apoptotic (pyknotic) forms.
LY-WZ	Lymphocyte cell size – distribution width	Higher values indicate greater variation in lymphocyte size, relative to LY-Z.
MO-X	Monocyte cell complexity	Increases with more granules, vacuoles, or inclusions; decreases when monocytes exhibit simpler internal morphology.
MO-WX	Monocyte complexity – distribution width	Higher values denote greater heterogeneity in monocyte complexity, relative to MO-X.
MO-Y	Monocyte fluorescence intensity	Reflects cellular RNA and DNA content; elevated values are typical of activated monocytes or monoblasts.
MO-WY	Monocyte fluorescence intensity – distribution width	Represents the degree of heterogeneity in nucleic acid content across the monocyte population, compared with MO-Y.
MO-Z	Monocyte cell size	Indicates average monocyte volume; changes may reflect abnormal cell enlargement or shrinkage.
MO-WZ	Monocyte cell size – distribution width	Higher values correspond to greater variation in monocyte size, relative to MO-Z.